REMARKS

Claims 1-52 are pending in the application.

Claims 1-52 are rejected.

Claims 1-24, 27-42, 46, 47, and 49-52 are original.

Claims 43-45 are amended.

Claims 25, 26, and 48 are cancelled.

Original Claims 1-24, 27-42, 46, 47, and 49-52 and amended Claims 43-45 are directed to compounds that are fused pyrimidinone derivatives, pharmaceutical compositions comprising the compounds, and methods of using comprising administering the compounds, and would be all of the claims pending in the application if the instant amendment is entered. No new matter is added.

Applicants respectfully request replacement of the currently pending Abstract and claim set with the above-amended Abstract and claim set.

Discussion of Amendments

The Abstract has been amended by deleting the definitions of the groups Y, R^1, R^4, X, A, B, R^2, and R^3 and instead incorporating their definitions from the specification.

Claims 43-45 are amended to delete the definition of Y. The definition of Y in Claims 43-45 was inadvertently carried over from Claims 41 and 42, as there is no Y group in a compound of Formula III, IV, or V according to Claims 43-45, respectively.

Applicants preserve their right to pursue the subject matter of cancelled claims and subject matter deleted from the claims by the above amendments in divisional, continuation, and continuation-in-part applications.

Abstract

In item 1. of the Office Action, the Examiner objected to the abstract because allegedly "it is longer than 15 lines or 150 words ." The abstract has been amended to reduce its length to 15 lines and 150 words, or less, rendering this objection moot.

Claim Rejections - 35 USC § 101

In item 2. of the Office Action, Claims 1-28 and 41-48 are rejected under 35 U.S.C. § 101 because allegedly "the claimed invention is not supported by either a specific asserted utility or a well established utility."

Applicants respectfully traverse this rejection for the reasons provided below. Applicants point out that the Utility Examination Guidelines issued by the USPTO ("Guidelines") do not require that an utility be "well-established" in order to satisfy the requirements of 35 U.S.C. § 101 (see section II(B)(2)(a)(2)(c)). Rather, utility of statutory subject matter must be specific, substantial, and credible to a person of ordinary skill in the art (see section II(B)(1)(c)).

Regarding the rejection of compound Claims 1-22 and 41-45, composition Claims 23-24 and 46-47, and method of treating a disease mediated by an MMP-13 enzyme Claims 27 and 28, Applicants respectfully point out to the examiner that the subject matter of said claims has an asserted utility related to inhibiting MMP-13 that is treating, for example, osteoarthritis (see page 1, at line 18, to page 2, at line 4, of the instant specification). Further, a person of ordinary skill in the art at the time the instant application was filed ("Skilled Artisan") knew that osteoarthritis was linked to interstitial collagen tissue degradation. Further support for treating osteoarthritis with an MMP-13 inhibitor is thus found on page 2, at lines 13-19, of the instant specification. Still further, the instant specification discloses treating breast cancer as another utility related to inhibiting MMP-13

(see page 2, at lines 19-22). Accordingly, the compounds of Claims 1-22 and 41-45, the compositions of Claims 23-24 and 46-47, and the methods of Claims 27 and 28 do have a specific and substantial utility relating a specific disorder in the specification to the inhibition of MMP-13 enzymes. Accordingly, Applicants deem that Claims 1-24, 27, 28, and 41-47 are patentable under 35 U.S.C. § 101.

Regarding the rejection of method of inhibiting MMP-13 enzyme Claims 25, 26, and 48, Claims 25, 26, and 48 have been cancelled, rendering the rejection with respect to these claims moot.

In view of the cancellation of Claims 25, 26, and 48 and the above remarks, Applicants deem that rejection of Claims 1-28 and 41-48 under 35 U.S.C. § 101 has been overcome.

Claim Rejections - 35 USC § 112, 2nd Paragraph

In item 3. of the Office Action, Claims 25, 26, 43-45, and 48 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

Applicants respectfully traverse this rejection for the reasons provided below.

Claims 25, 26, and 48 have been cancelled, rendering the rejection with respect to these claims moot.

Claims 43-45 have been amended to delete the objected to definition of Y.

In view of the cancellation of Claims 25, 26, and 48, the amendment of Claims 43-45, and the above remarks, Applicants deem that rejection of Claims

25, 26, 43-45, and 48 under 35 U.S.C. § 112, second paragraph, has been overcome.

Claim Rejections - 35 USC § 112, 1st Paragraph

In item 4 of the Office Action, Claims 27-40 and 49-52 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly "failing to comply with the enablement requirement."

Applicants respectfully traverse this rejection for the reasons provided below. The rejected claims are methods of treating diseases mediated by an MMP-13 enzyme.

The rejection is based on the allegation that an in vivo test is required "to show that the claimed compounds can treat any disorders" and that the skilled clinician cannot "apply the claimed compounds in a clinical setting without undue experimentation." Applicants will show below that there is considerable direction and guidance in the instant specification for practicing the invention of Claims 27-40 and 49-52, that all of the methods of practicing the invention of Claims 27-40 and 49-52 were well known, and that the level of the Skilled Artisan was high. Accordingly, no undue experimentation is required to practice the instant invention, and thus an in vivo test is not a proper requirement for patentability of the invention of Claims 27-40 and 49-52 under 35 U.S.C. § 112, first paragraph, and is contrary to MPEP § 2164.01(a).

At the time the instant application was filed, it was well known in the art that MMP-13 enzymes mediated a number of disease pathologies, including osteoarthritis, rheumatoid arthritis, and cancer. See, for example, U.S. Patent No. 6,008,243 (issued December 28, 1999) in column 1, at lines 53-58, and column 2, at lines 23 to 46, and references cited on page 2, second column, Freije et al., "Molecular Cloning and Expression of Collagenase-3, a Novel Human Matrix

Metalloproteinase Produced by Breast Carcinomas," *The Journal of Biological Chemistry*, vol. 269, No. 24 (1994), pp. 16766-16773; and Mitchell et al., "Cloning, Expression, and Type II Colagenolytic Activity of Matrix Metalloproteinase-13 from Human Osteoarthritic Cartilage," *The Journal of Clinical Investigation*, vol. 97, No. 3 (1996), pp. 761-768 (COPIES ENCLOSED WITH THE INFORMATION DISCLOSURE STATEMENT ("IDS")).

Further as the Examiner admits, an "*in-vivo* test is not a requirement for enablement." In fact, it was well established that in vitro activity recognized by the Skilled Artisan as correlating with an invention method was sufficient to satisfy the enablement requirement under 35 U.S.C. §112. A rigorous or an invariable exact correlation between in vitro data and in vivo efficacy is not required. (See MPEP 2164.02 under the heading "CORRELATION:*IN VITRO/IN VIVO*."). Nor is clinical data required, as the court addressed in In re Brana, 34 USPQ2d 1437 (CAFC 1995), where the court said:

> "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas . . . ". (34 USPQ2d at 1442-1443).

In the instant case, the Skilled Artisan knew the positive MMP-13 IC_{50} inhibitory data in Table I on pages 198 to 210 of the instant specification. These data teach the concentration of invention compound required to inhibit an MMP-13 enzyme's activity by 50% and show that the invention compounds are inhibitors of the enzyme.

The Skilled Artisan also knew that a number of MMP inhibitors had shown efficacy in vivo and had been the subjects of clinical trials (see Beckett, et

al., "Matrix metalloproteinase inhibitors 1998," *Expert Opinions Ther. Patents*, 1998;8(3):260, COPY ENCLOSED WITH IDS).

Further, the instant specification on page 213, at line 31, to page 214, at line 17, teaches the Skilled Artisan methods for determining dosages effective for treating a MMP-13 mediated disease, and how to initiate treatment and titrate to an effective dosage. The instant specification also teaches specific dosage ranges (see page 214, at lines 5-7 and 14-17).

Further, the instant specification on page 211, at line 7, to page 216, at line 4, teaches the Skilled Artisan how to formulate and administer an invention pharmaceutical composition.

Further, the level of skill of the Skilled Artisan, who is typically a Ph.D. or M.D. (e.g., the Examiner's "skilled clinician"), is high, and thus the teaching requirements to avoid undue experimentation is low.

Still further, enablement predicated on an invention compound having to have structural similarity to an art recognized compound with the same or similar utility may be required when the specification is silent with respect to dosages (MPEP § 2164.06(b) under the heading SEVERAL DECISIONS RULING THAT THE DISCLOSURE WAS ENABLING). However as discussed above, the instant specification teaches dosages, and thus it is improper in the instant rejection to apply such an enablement requirement to instant Claims 27-40 and 49-52.

As shown by the above remarks, the skilled artisan knew that the pathologies of MMP-13 mediated diseases had in common this common mechanism and that the compounds of the instant invention were inhibitors of MMP-13. The Skilled Artisan also knew that a correlation existed between in

vitro inhibition of MMP enzymes and pharmacological activity against MMP-mediated diseases. The Skilled Artisan also knew how to determine proper dosages, formulate the invention compounds and administer them to a patient without undue experimentation. Accordingly, the Skilled Artisan would know without undue experimentation and without an in vivo test how to use a compound of the instant invention for treating cancer metastasis and angiogenesis, osteoarthritis, rheumatoid arthritis, heart failure, inflammation, and other MMP-13 mediated diseases.

In view of the above remarks, Applicants deem that rejection of Claims 27-40 and 49-52 under 35 U.S.C. § 112, first paragraph, is overcome.

Information Disclosure Statement

In regard to item 5 of the Office Action, Applicants thank the Examiner for her telephonic conversation on September 8, 2003, whereby it was agreed that Applicants would submit the instant papers without providing replacement copies of the references cited in their IDS of June 10, 2002. Further, the Examiner kindly agreed to promptly look again for the missing copies of the references. In a telephonic conversation on September 11, 2003, the Examiner reported that the copies of the references sill could not be located. The Examiner kindly agreed to look again for them after receiving the instant papers. If said copies still cannot be found, the Examiner agreed to contact the undersigned, and Applicants will then submit replacement copies, at least of the non-patent art. Accordingly, Applicants respectfully request notification of the need for said replacement copies in good time for the Examiner to consider them before issuing her next Office Action.

References cited on PTO-892

In regard to item 6 of the Office Action, Applicants acknowledge receipt of PTO-892 and thank the Examiner for copies of the references cited therein.

Supplemental Information Disclosure Statement

Applicants bring to the Examiner's attention the enclosed Supplemental Information Disclosure Statement on Form PTO-1449, which cites WO 00/09485, WO 01/12611, WO 02/34726, WO 02/34753, EP 0,935,963, EP 1,138,680, Freije et al. 1994, Mitchell et al. 1996, and Beckett et al., 1998. The Examiner is respectfully requested to consider carefully the references cited therein in connection with the examination of the above-identified application in accord with 37 CFR §1.104(a). It is believed the Examiner will concur with Applicant's belief that the subject matter presently claimed is neither claimed in nor obvious from these references.

It is further respectfully requested that the references listed on the enclosed Form PTO-1449 be included in the "References Cited" portion of any patent issuing from this application (MPEP § 1302.12).

Benefit of Priority Under 35 U.S.C. § 119(e)

Applicants note with pleasure the acknowledgement of their claim for domestic priority under 35 U.S.C. § 119(e).

Applicants note to the Examiner that the Transmittal of a Patent Application under 37 C.F.R. 1.53(b) contained a request to insert their claim for domestic priority in the specification. Accordingly, Applicants have not amended the specification in this paper to insert a cross-reference to the related U.S. provisional application.

Conclusion

In view of the amendment of the Abstract and Claims 43-45, cancellation of Claims 25, 26, and 48, and the above remarks, Applicants deem that original Claims 1-24, 27-42, 46, 47, and 49-52 and amended Claims 43-45 are in

condition for allowance. Applicants respectfully request the Examiner to promptly reconsider these claims and pass patentable claims to allowance.

The Commissioner is hereby authorized to charge any fees that may be required, or credit any overpayment, to deposit account number 23-0455.

The undersigned would welcome a telephone call from the Examiner to discuss any matters related to this case that the Examiner thinks are amenable to resolution by such discussion.

Respectfully submitted,

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